# Improvement in Wearing-Off Effect Correlates with Increased Tregs and Decreased Inflammatory Monocytes After Switch to Ublituximab in the ENHANCE Study

Gabriel Pardo[1], Hari Miskin[2], Christopher Rowland[2], Emmanuel Normant[2],and Anne Gocke[2]

[1]Oklahoma Medical Research Foundation, Oklahoma City, United States, [2]TG Therapeutics, Morrisville, United States

## OBJECTIVE

- To characterize changes in immune cell phenotypes and corresponding changes in treatment satisfaction questionnaire for medication (TSQM-9) before and after switch from ocrelizumab to ublituximab among participants in the ENHANCE study who reported symptomatic wearing-off but remained B-cell depleted (<10 cells/μL) during prior ocrelizumab therapy.

## OVERVIEW IN BRIEF

- This study aimed to compare immunophenotypes of monocyte and T-cell populations in participants with MS who were clinically stable and B cell depleted but reported wearing off prior to switching from ocrelizumab to ublituximab in the ENHANCE study.
- Peripheral Blood Mononuclear Cells (PBMCs) from 10 participants who reported wearing-off and 10 participants who did not report wearing off on ocrelizumab were analyzed ex-vivo by flow cytometry at baseline (D1) and 12 weeks after switching to ublituximab (W12).
- TSQM-9 was administered to both groups just prior to the Week 24 infusion with ublituximab.
- Demographics, baseline characteristics, changes in immunophenotyping at Baseline and Week 12, and TSQM-9 results from Week 24 are presented herein.
- Increases in CD4+ regulatory T-cells and corresponding decreases in inflammatory monocytes were observed at Week 12 and treatment satisfaction was near 100% at Week 24 in both groups after switching to ublituximab.

## CONCLUSION

- The wearing-off phenomenon may be attributable to residual inflammation even in the context of persistent peripheral B-cell depletion. Shifts in immune cell phenotypes, such as CD4+ regulatory T-cells and monocytes, toward an anti-inflammatory composition offer a potential mechanism by which ublituximab can attenuate wearing-off and improve treatment satisfaction.

REFERENCES:

1. Dhib-Jalbut, S. Neurotherapeutics. 2026; 23 (1) e00824.
2. Yakubu, A., et al. Mult. Scler. Relat. Disord. 2025; 102:106619.
3. Marian, LM., et al. Mult Scler J Exp Transl Clin. 2024; 10(2):20552173241251707.
4. M. Seferoğlu, et al. Mult. Scler. Relat. Disord. 2024; Dec:92:105939.
5. A.A. Toorop, et al. Mult. Scler. Relat. Disord. 2022; Jan:57:103364.
6. Kister I., et al. Neurol Clin Pract. 2023;13:e200185.
7. Monteiro I., et al. J Neurol. 2024; Aug;271(8):5012-5024.
8. Steinman L., et al. N Engl J Med. 2022;387(8):704-714.

ACKNOWLDGEMENTS:

The authors thank the participants and their families for their contributions to the study and Victoria Findlen for editorial support.

DISCLOSURES:

Gabriel Pardo has received research grants (to the institution) from Biogen, EMD Serono, Roche/Genentech, Sanofi Genzyme, Novartis, AbbVie, TG Therapeutics, and BMS; consultant and/or speaker bureau for Biogen, EMD Serono, Roche/Genentech, Sanofi Genzyme, Novartis, Janssen, BMS, TG Therapeutics, Horizon Therapeutics, Alexion Pharmaceuticals, PRIME Education, and MSAA. Hari Miskin, Christopher Rowland, Emmanuel Normant, and Anne Gocke are all employees of and hold stock or stock options in TG Therapeutics, Inc.

## BACKGROUND

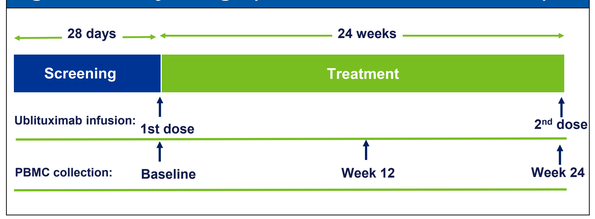
- People with multiple sclerosis (PwMS) commonly transition between disease modifying therapies (DMTs) to address suboptimal response to treatment, tolerability concerns, or for patient convenience.[1]
- Among the most common reasons for switching is the wearing-off phenomenon, which is described as transient worsening of MS symptoms at the end of the dosing interval.[2-3]
- The “wearing-off” phenomenon is increasingly recognized, particularly among people treated with monoclonal antibody therapies, but whether it is a true pharmacologic/immune phenomenon or can be attributed to fluctuations in chronic MS symptoms is still debated.[2-3]
- Previous studies found no relationship between wearing-off and CD19+ B-cell repopulation, infusion interval, MRI activity, relapses, or EDSS.[4-6]
- However, a recent study demonstrated an association between increased severity of wearing-off in PwMS treated with ocrelizumab and increases in inflammatory CD8+ T-cells that correlate with higher sNfL, suggesting a role for reduced immunomodulation.[7]
- Ublituximab is a novel monoclonal antibody targeting a unique epitope on CD20 and is glycoengineered for enhanced antibody-dependent- cell-mediated cytotoxicity.[8]
- The impact of switching from one anti-CD20 mAb to another on the immunomodulatory response in PwMS experiencing the wearing-off phenomenon is unknown.

## METHODS

- PwMS on ocrelizumab who were clinically stable with sustained B-cell depletion, but reported wearing-off were switched to ublituximab as part of the ENHANCE study.
- Participants transitioned from ocrelizumab and were required to remain B-cell depleted prior to initiation of ublituximab for inclusion in the analysis.
- Participants received 450 mg ublituximab on Day 1, followed by 450 mg at Week 24.
- Participants with and without self-reported wearing-off at baseline with matched demographics were selected for analysis of immune cell phenotypes (n=10 per group).
- T-cells and myeloid cells were examined using multi-color flow cytometry at baseline and at Week 12 post switch to ublituximab.
- Changes in TSQM-9 at Week 24 were also assessed in both groups.

## RESULTS

### Figure 1. Study Design (ENHANCE PBMC collection)



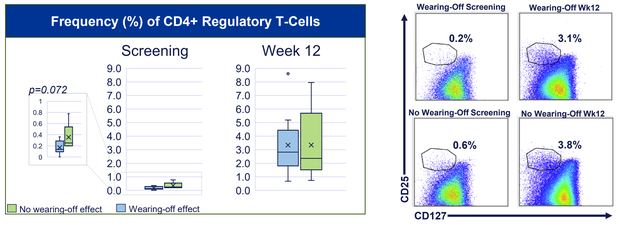

- Participants receiving ocrelizumab for treatment of relapsing MS with B cell counts of <10 cells/μL were selected for inclusion in cohorts 1 and 2 of the ENHANCE study. Participants either reported wearing off (wearing-off group) or did not report wearing off (no wearing-off group). Ublituximab was infused at D1 and W24. PBMCs from both groups were collected at Baseline, W12, and W24 and cryopreserved for future use **(Figure 1).**

### Table 1. Demographics

| | Wearing-Off (n=10) | No Wearing-Off (n=10) |
|---|---|---|
| **Age** (years) | 42.8 (23-63) | 41.6 (25–60) |
| **Sex** n(%) | | |
| Male | 3 (30) | 3 (30) |
| Female | 7 (70) | 7 (70) |
| **Race** n(%) | | |
| Caucasian | 9 (90) | 9 (90) |
| **Ethnicity** n(%) | | |
| Not Hispanic or Latino | 10 (100) | 10 (100) |
| **Prior treatment,** n (%) | | |
| Ocrelizumab | 10 (100) | 10 (100) |
| Time to last dose (months) | 6 | 6 |

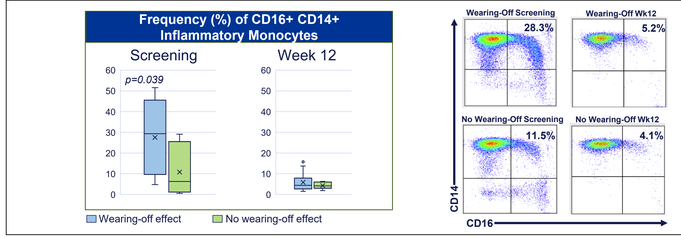
- Participants from both groups were closely matched for baseline demographics. Age, Sex, Race, Ethnicity and prior treatment are described **(Table 1).**

### Figure 2. CD4+CD25+CD127lo Tregs Increased After Switch to Ublituximab in People With and Without Wearing-Off at Baseline




- Wearing-off on ocrelizumab was associated with a decrease in the frequency of CD4+CD25+CD127lo regulatory T-cells (0.2% vs 0.4%) at screening. 12 weeks after switching to ublituximab, in both groups, CD4+ Treg frequencies were significantly increased (3.4% vs 3.5%) (left panel). Representative flow cytometry plots from 1 participant experiencing wearing-off and 1 participant without wearing-off are shown at Baseline and at Week 12 (right panel) **(Figure 2)**.

### Figure 3. CD14+CD16+ Inflammatory Monocytes Decrease After Switch to Ublituximab In People With and Without Wearing-Off at Baseline




- Wearing-off on ocrelizumab was associated with significantly increased CD14+CD16+ inflammatory monocytes at screening (27.5% vs 10.8%). 12 weeks after switching to ublituximab, CD14+CD16+ monocytes were decreased and similar in both groups (5.88% vs 4.29%) (left panel). Representative flow cytometry plots from 1 participant experiencing wearing-off and 1 participant without wearing-off are shown at baseline and at Week 12 (right panel) **(Figure 3)**.

### Figure 4a. TSQM-9 Response Rates in People With Baseline Wearing-Off at Week 24 After Switch to Ublituximab

### Figure 4b. TSQM-9 Response Rates in People Without Baseline Wearing-Off at Week 24 After Switch to Ublituximab

- Changes in Tregs and inflammatory monocytes correlated with participants reporting overall satisfaction with ublituximab when assessed just prior to their Week 24 infusion. Overall, 95% (19/20) of participants responded positively to all 9 questions and satisfaction was consistent at Week 24 regardless of baseline wearing-off status **(Figure 4a and 4b)**, supporting an overall high level of treatment satisfaction with ublituximab.

Presented at the 10th Joint ACTRIMS-ECTRIMS Meeting | 21-23 October 2026 | Toronto, Canada | P1419